

PRIOR AUTHORIZATION POLICY

POLICY: Oncology – Cabometyx™ (cabozantinib tablets – Exelixis Inc.)

TAC APPROVAL DATE: 01/23/2019

OVERVIEW

Cabometyx is a kinase inhibitor indicated for the treatment of patients with advanced renal cell carcinoma (RCC).¹ It is also indicated for the treatment of patients with hepatocellular carcinoma (HCC) who have been previously treated with Nexavar® (sorafenib tablets). *In vitro* biochemical and cellular assays have shown Cabometyx to inhibit the tyrosine kinase activity of rearranged during transfection (RET), MET, vascular endothelial cell growth factor receptor (VEGFR)-1, -2, and -3, KIT, tyrosine-related kinase B (TrkB), c-ros oncogene 1 (ROS1), TYRO3, MER, Fms-like tyrosine kinase 3 (FLT-3), AXL, and TIE-2. These receptor tyrosine kinases are involved in both normal cellular function and pathologic processes such as oncogenesis, metastasis, tumor angiogenesis, drug resistance, and maintenance of the tumor microenvironment.

Guidelines

In the National Comprehensive Cancer Network (NCCN) clinical practice guidelines for kidney cancer (version 2.2019 – September 17, 2018), the recommendations for first-line oral therapy regimens in favorable risk patients with relapsed or Stage IV RCC with predominant clear cell histology are: Sutent® (sunitinib malate capsules), Votrient® (pazopanib tablets) [both category 1, preferred], Inlyta® (axitinib tablets) [category 2B], and Cabometyx (category 2B).² For patients in the poor/intermediate risk grouping, the preferred oral regimen is Cabometyx (category 2A), although Sutent and Votrient are category 1 recommended therapies in this grouping. Inlyta is a category 2B agent that is useful under certain circumstances. Recommendations for subsequent oral therapies include Cabometyx (category 1, preferred), Inlyta (category 1), Lenvima™ (lenvatinib capsules) + Afinitor® (everolimus tablets) [category 1]; Afinitor, Sutent, or Votrient are all category 2A recommended therapies. Nexavar is a category 2B recommended option that can be useful under certain circumstances. For patients with non-clear cell histology RCC, Sutent and enrollment in clinical trials are noted as preferred therapies (category 2A, preferred); Cabometyx and Afinitor are other recommended regimens; Inlyta, Lenvima + Afinitor, Votrient, Tarceva® (erlotinib tablets), Avastin + Tarceva, and Avastin + Afinitor are the other recommended options (all category 2A). In addition to the first-line systemic therapy option, Sutent is also recommended as adjuvant therapy after primary treatment (e.g., nephrectomy, active surveillance) in high-risk patients with clear cell RCC (category 2B).

The NCCN hepatobiliary cancers (version 1.2019 – December 17, 2018) recommends Nexavar and Lenvima as preferred first-line systemic therapy options.³ Nexavar is a category 1 recommended option for Child-Pugh Class A or category 2A recommendation for Child-Pugh Class B7. Lenvima is a category 2A recommendation for Child-Pugh Class A only. The following are subsequent therapy options if there is disease progression: Stivarga (regorafenib tablets) [Child-Pugh Class A only; Category 1], Cabometyx (Child-Pugh Class A only; Category 1), Cyramza® (ramucirumab for intravenous injection) [Category 1], Opdivo (nivolumab for intravenous injection) [Child-Pugh Class A or B7; Category 2A], Nexavar (after first-line Lenvima; Category 2A), and Keytruda (pembrolizumab for intravenous injection) [Category 2A].

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Cabometyx. All approvals are provided for 3 years in duration unless otherwise noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Cabometyx is recommended in those who meet the following criteria:

FDA-Approved Indication

- 1. Renal Cell Carcinoma (RCC), Advanced (Predominant Clear Cell or Non-Clear Cell Histology).**
Approve for 3 years.
- 2. Hepatocellular Carcinoma.** Approve for 3 years if the patient has been previously treated with at least one tyrosine kinase inhibitor therapy (e.g., Nexavar[®] (sorafenib tablets), Lenvima [lenvatinib capsules]).

Other Uses with Supportive Evidence

- 3. Non-Small Cell Lung Cancer with RET Gene Rearrangements.** Approve for 3 years.

The NCCN Non-Small Cell Lung Cancer (NSCLC) guidelines (version 3.2019 – January 18, 2019) recommend cabozantinib for RET gene rearrangements (category 2A).⁴ This is based on results from a small case series and a Phase II study in 25 patients.⁵⁻⁶ Cabometyx 60 mg dose was used in the case series and the Phase II study. In the Phase II study, the rate of partial response was 28% and the median duration of response was 7.0 months.⁶ At the time of data cutoff, 76% of the patients either had disease progression or died. The median progression-free survival (PFS) was 5.5 months and the median overall survival was 9.9 months.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Cabometyx has not been shown to be effective, or there are limited or preliminary data or potential safety concerns that are not supportive of general approval for the following conditions. Rationale for non-coverage for these specific conditions is provided below. (Note: This is not an exhaustive list of Conditions Not Recommended for Approval.)

- 1. Metastatic Castration-Resistant Prostate Cancer (mCRPC).**

Results from the COMET-1 Phase III pivotal study with Cabometyx 60 mg tablets in men with mCRPC are published.⁷ Patients included in the study had disease progression after treatment with docetaxel as well as Zytiga[®] (abiraterone acetate tablets) and/or Xtandi[®] (enzalutamide capsules). The study failed to meet its primary endpoint of demonstrating statistically significant increase in overall survival (OS) compared with prednisone. The median OS with Cabometyx was 11.0 months vs. 9.8 months with prednisone (hazard ratio [HR] 0.90; 95% CI: 0.76, 1.06; P = 0.213). Based on these results, the second Phase III study, COMET-2 has been discontinued.⁸

- Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

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- The NCCN Kidney Cancer Clinical Practice Guidelines in Oncology (Version 2.2019 – September 17, 2018). © 2018 National Comprehensive Cancer Network, Inc. Available at: <http://www.nccn.org>. Accessed January 21, 2019.
- The NCCN Hepatobiliary Cancers Clinical Practice Guidelines in Oncology (Version 1.2019 – December 17, 2018). © 2018 National Comprehensive Cancer Network, Inc. Available at: <http://www.nccn.org>. Accessed January 21, 2019.
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- Smith M, De Bono J, Sternberg C, et al. Phase III study of cabozantinib in previously treated metastatic castration-resistant prostate cancer: COMET-1. *J Clin Oncol*. 2016;34:3005-3013.
- Exelixis. Study of cabozantinib (XL184) versus mitoxantrone plus prednisone in men with previously treated symptomatic castration-resistant prostate cancer (COMET-2). In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2000- [cited 2017 April 18]. Available from: <http://www.clinicaltrials.gov/ct2/show/NCT01522443?term=NCT01522443&rank=1>. NLM identifier: NCT01522443 (terminated).

HISTORY

Type of Revision	Summary of Changes*	TAC Approval Date
Annual revision	New policy	05/04/2016
Selected revision	Added approval condition for Cabometyx in non-clear cell histology RCC based on NCCN guidelines.	10/12/2016
Annual revision	No criteria changes	04/26/2017
Selected revision	Added new approval criteria under Other Uses with Supportive Evidence for use of Cabometyx in first-line setting. Added “Subsequent Therapy” qualifier to criteria #1.	09/27/2017
Early annual revision	Combined the two approval conditions for Cabometyx use in first-line setting and subsequent therapy setting due to the new FDA-approval in first-line setting. Of note, for patients with predominant clear cell histology, the requirement that the patient has tried one tyrosine kinase inhibitor in the subsequent therapy setting was removed, and for the first-line setting the requirement that the patient is in the intermediate- or poor-risk group according to the prescribing physician, was removed.	01/03/2018
Annual revision	Added new approval condition for hepatocellular carcinoma based on FDA-approval.	01/23/2019

TAC – Therapeutic Assessment Committee; DEU – Drug Evaluation Unit; * For a summary of criteria changes, refer to respective TAC minutes available at: <http://esidepartments/sites/Dep043/Committees/TAC/Forms/AllItems.aspx>.